

Occupation and Leukemia: A Population-Based Case±Control Study in Iowa and Minnesota

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Background Studies have suggested that risk of leukemia may be associated with occupational or industrial exposures and risk may vary by the histological type of the disease.

Methods A population-based case±control study was conducted in Iowa and Minnesota to evaluate the association between various occupations, industries, and occupational exposures and leukemia risk. A total of 513 cases and 1,087 controls was included in the study. A lifetime occupational history and other risk factor information were collected through in-person interviews, and a job-exposure matrix was used to assess possible risks associated with specific exposures.

Results A significantly increased risk of leukemia was observed among agricultural service industries and among nursing and healthcare workers. Janitors, cleaners, and light truck drivers also experienced increased risk. Those employed in plumbing, heating and air conditioning industries, and sales of nondurable goods (such as paints and varnishes) had an increased risk. Printers, painters, and workers in the food and metal industries had a nonsignificantly increased risk of leukemia. Analyses by specific exposures and histology of leukemia showed that risk of leukemia associated with occupational or industrial exposures may vary by histological type of the disease.

Conclusions An increased risk of leukemia among workers employed in agricultural industries, nursing and healthcare workers, and in a few occupations with possible exposure to solvents is consistent with earlier studies. Associations of risk with occupations not observed previously deserve further assessment. *Am. J. Ind. Med.* 40:3±14, 2001. Published 2001 Wiley-Liss, Inc.[†]

KEY WORDS: leukemia; industry; occupation; nursing; health care work; solvents; agriculture; janitors; metal industries; myelodysplasia

INTRODUCTION

Although ionizing radiation, benzene, and alkylating agents are established causes of leukemia, these known risk

factors explain only a small proportion of cases, and the overall etiology of this cancer is still largely unknown [Zeeb and Blettner, 1998]. Pesticides, hair dyes, smoking, diet, solvents, and viral exposures have also been suggested as risk factors for leukemia, as noted in recent reviews [Blair and Zahm, 1995; Linet and Cartwright, 1996; Dich et al., 1997; and Zeeb and Blettner, 1998].

Several lines of evidence suggest that occupational exposures could play a role in the development of leukemia: the male excess, the consistent increase among older males in many geographic areas, the higher incidence of acute myeloid leukemia in developed countries and industrial metropolitan areas in the US, and the presence of known and

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Accepted 21 February 2001

suspected hazardous agents in the workplaces [Linnet and Cartwright, 1996]. Employment in many industries and occupations has been associated with leukemia including agriculture [Blair and Zahm, 1995; Kristensen et al., 1996; Cerhan et al., 1998], oil refining and petrochemicals [Jarvholm et al., 1997; Divine et al., 1999], construction [Robinson et al., 1995, 1999], and the nuclear industry or weapons production [Kendall et al., 1992; Cardis et al., 1995]. Elevated risk of leukemia has also been observed among nurses and other healthcare workers [Peipins et al., 1997; Burnett et al., 1999; Petralia et al., 1999], electric utility workers [London et al., 1994; Floderus et al., 1999], vehicle mechanics [Hunting et al., 1995], managers and professionals [Loomis and Savitz, 1991], hairdressers [Miligi et al., 1999], shoe manufacturing workers [Bulbulyan et al., 1998], painters and printers [Lloyd et al., 1977; Lindqvist et al., 1987], welders [Stern et al., 1986] and embalmers, anatomists, and pathologists [Linos et al., 1989; Hayes et al., 1990].

Some occupational exposures appear to be related to specific histological types of leukemia. Benzene is primarily associated with the risk of acute myeloid leukemia (AML) [IARC, 1981]. Welding has been associated with an increased risk of chronic myeloid leukemia (CML) [Preston-Martin and Peters, 1988] asbestos exposures has been related to an increased risk of chronic lymphocytic leukemia (CLL) [Schwartz et al., 1988], and carpet manufacturing was associated with a higher risk of lymphocytic leukemia [O'Brien and Decoupe, 1988]. On the other hand, farming has been associated with an increased risk of many types of leukemia including acute lymphocytic leukemia (ALL), CLL, CML and AML [Donham et al., 1980; Blair and White, 1981, 1985; Brown et al., 1990]. These suggestive associations require further examination. To provide further insight into the role of occupation and occupational exposures, and risk of leukemia by histological type, we analyzed data from a population-based case-control study in Iowa and Minnesota.

MATERIALS AND METHODS

As reported elsewhere [Brown et al., 1990], this population-based case-control study included all cases of leukemia diagnosed among white men, 30 years of age or older, identified from the Cancer Registry of Iowa between March 1981 and October 1983, and all cases of leukemia identified between October 1980 and September 1982 from a surveillance network of hospitals in Minnesota covering 97% of the hospital beds available in that state. The major purpose of this study was to evaluate agricultural risks, therefore, cases and controls residing in Minneapolis, St. Paul, Duluth, and Rochester were excluded. We identified 669 eligible cases, and 578 (86%) participated in the study. Interviews were conducted with 340 leukemia cases and 238

surrogates for deceased subjects or those too ill to interview. The diagnosis of leukemia for all cases was confirmed by pathology review.

A total of 1245 population-based controls was frequency-matched to cases by 5-year age group, vital status at the time of the interview, and state of residence. Four hundred and seventy-four controls for cases less than 65 years of age were selected by random digit dialing [Waksberg, 1978], 519 controls for cases 65 years or older were selected from listings provided by the Health Care Financing Administration, and 550 controls for deceased cases were selected from state death certificates. Response rates were 77% for random digit dialing controls (telephone screener response rate (87.5%) of interview response rate (88%)), 79% for Health Care Financing Administration controls, and 77% for surrogate respondents for deceased subjects.

Interviews were conducted between 1981 and 1984 using a standardized and structured questionnaire. Interviews averaging about 50 min gathered information on lifetime farm and non-farm occupational history. The occupational history included each job held for more than 1 year, the industry where employed, and starting and ending year the job was held. Job titles and industries were classified according to the Dictionary of Occupational Titles (DOT) [US Department of Labor, 1977] and Standard Industrial Classification Codes (SIC) [Office of Management and Budget, 1979]. Information was also collected on residential history, drinking water sources, smoking and alcohol use, medical history, family history of cancer, education, and other demographic variables.

A job-exposure matrix for selected occupational exposures was developed for coded DOT/SIC combinations by one of us (PAS). Exposure assignments were based on typical exposure characteristics of the job and made without knowledge of case/control status. Intensity and probability of exposure were assessed for benzene, other organic solvents, petroleum-based oils and greases, cooking oils, ionizing radiation, paper dusts, gasoline and diesel vapors and exhausts, paints, electromagnetic fields, metals (fumes and dusts), wood dusts, asbestos, formaldehyde, asphalt and other tar products, cattle, fresh meat, and solder fumes. Working with sick people or with children was also included as a specific type of exposure. These assessments were scored for all non-farming jobs.

Probability of exposure and intensity of exposure were each scored on a 4-point scale (i.e., for intensity: unexposed, low, moderate, and high exposure). Probability refers to the likelihood that a person in a particular job or industry was actually exposed to the substance of interest. Intensity of exposure refers to the level likely to be experienced in a particular job/industry if exposure actually occurs, and can be considered as an 8-time-weighted average over a year. The calendar year period for each job/industry

was considered when estimating the intensity and probability. For example, formaldehyde exposure in the plywood industry started in 1935 with the introduction of formaldehyde-based glues. The estimated intensity of exposure to formaldehyde was reduced after 1977 when the plywood industry reduced the formaldehyde concentration in plywood glues.

Risks for leukemia associated with various occupations, industries, and occupational exposures were calculated using unconditional logistic regression models. A polychotomous model was used when the association by histologic type of leukemia was considered because the same set of study controls ($N = 1245$) was used for each type of leukemia. Odds ratios (ORs) and 95% confidence intervals (95% CI) were calculated using SAS statistical software [SAS, 1990]. ORs were calculated for all 2-digit and 3-digit DOT codes and SIC codes, as well as for specific exposures from the job-exposure matrix. Other factors included in the model were age (< 45 , 45 ± 64 , $65 \pm$), state of residence (Iowa or Minnesota), direct or surrogate respondent status, agricultural use of pesticides (ever, never), postsecondary education (yes, no), personal use of hair dyes (ever, never), first degree relative with a lymphatic or hematopoietic tumor (yes, no), and tobacco smoking (ever, never). Risk of leukemia was evaluated by duration of employment in various DOT and SIC categories (< 10 , ≥ 10 years), and by intensity and probability of exposure to

various chemicals. In the analyses by intensity, we combined the highest two exposure strata to create a three-level scale. An index variable was created by multiplying intensity of exposure by duration of exposure in order to develop an estimate of cumulative exposure. Analyses by year of first exposure were also conducted to evaluate latency. The comparison category for all analyses was composed of subjects not employed in the occupation or industry of interest, or those lacking the specific exposure being evaluated.

RESULTS****

Because leukemia has been shown to be elevated among farmers in this study [Brown et al., 1990], subjects whose sole occupation was farming were excluded, leaving 513 cases and 1087 controls available for this analysis. The number of leukemia cases by histology was: 214 (41.7%) CLL, 132 (25.7%) AML, 46 (9.0%) CML, 13 (2.5%) ALL, 58 (11.3%) myelodysplasia, and 50 (9.8%) others.

As shown in Table I, several broad industries and occupational categories were significantly associated with leukemia risk either overall or in one of the duration categories. These include agricultural services; plumbing, heating, and air conditioning; sales of nondurable goods (e.g., paints, varnishes, and supplies); real estate operators and lessors; amusement and recreation services; health

TABLE I. Statistically Significant Associations Between Leukemia and Duration of Employment by Industry or Occupation Among Cases and Controls From Iowa and Minnesota

Job title (DOT code)	All subjects		< 10 years		≥ 10 years	
	Ca/Co	OR ^a (95%CI)	Ca/Co	OR ^a (95%CI)	Ca/Co	OR ^a (95%CI)
Industry						
Agricultural services (7)	20/34	1.2 (0.7/2.1)	5/18	0.5 (0.2/1.5)	14/14	2.1 (1.0/4.5)
Plumbing, heating, and air conditioning (171)	15/18	1.7 (0.8/3.5)	11/2	11.8 (2.6/54)	4/14	0.6 (0.2/1.8)
Miscellaneous nondurable goods (519)	17/16	2.3 (1.2/4.7)	9/8	2.5 (1.0/6.7)	8/8	2.1 (0.8/5.8)
Real estate operators and lessors (651)	7/4	3.5 (1.0/12.1)	3/3	1.9 (0.4/9.8)	4/1	8.2 (0.9/75)
Miscellaneous amusement and recreation services (799)	11/7	3.1 (1.2/8.1)	9/6	2.8 (1.0/8.1)	2/1	4.5 (0.4/51)
Health services (80)	28/33	1.8 (1.1/3.1)	13/13	2.1 (1.0/4.6)	14/18	1.8 (0.9/3.6)
Hospitals (806)	22/23	2.1 (1.1/3.8)	13/13	2.2 (1.0/4.9)	8/10	1.7 (0.6/4.3)
Miscellaneous services (89)	15/13	2.7 (1.2/5.7)	10/6	4.0 (1.4/11)	4/6	1.5 (0.4/5.2)
Accounting, auditing, and book-keeping (893)	8/6	2.8 (1.0/8.4)	4/2	4.5 (0.8/25.3)	3/4	1.5 (0.3/7.0)
Occupation						
Financial insurance and real estate managers (186)	13/11	2.9 (1.3/6.7)	6/4	3.5 (1.0/13)	7/7	2.4 (0.8/7.0)
Lodging and related service occupations (32)	7/5	2.8 (0.9/9.1)	7/4	3.6 (1.0/12)	0/1	
Miscellaneous personal service occupations (35)	12/12	2.3 (1.0/5.2)	11/11	2.2 (0.9/5.2)	1/1	2.0 (0.1/33.0)
Building and related service occupations (38)	41/71	1.2 (0.8/1.7)	17/47	0.7 (0.4/1.3)	23/24	1.9 (1.1/3.4)
Janitors (382)	27/35	1.6 (0.9/2.6)	8/22	0.7 (0.3/1.7)	18/13	2.8 (1.4/5.8)
Truck drivers, light (906)	13/8	3.4 (1.4/8.4)	11/8	3.0 (1.2/7.6)	2/0	

^aAdjusted for age, state of residence, proxy interview, post-secondary education, pesticides, hair dyes, smoking, and first degree relative with a lymphatic or hematopoietic tumor.

TABLE II. Risk ($OR^{\pm 2.0}$) of Leukemia by Duration of Employment in Industry (Based on Four or More Exposed Cases) Among Cases and Controls From Iowa and Minnesota

Industry (SI Code)	All subjects		< 10 years		≥ 10 years	
	Ca/Co	OR ^a (95%CI)	Ca/Co	OR ^a (95%CI)	Ca/Co	OR ^a (95%CI)
Metal mining (10)	15/21	1.5 (0.8/3.0)	5/6	2.0 (0.6/6.5)	10/15	1.3 (0.6/3.1)
Nonmetallic minerals, except fuels (14)	7/9	1.7 (0.6/4.5)	5/5	2.1 (0.6/7.3)	1/3	0.8 (0.1/7.4)
Masonry, stonework, tile, and plastering (174)	6/6	2.0 (0.6/6.3)	3/1	4.8 (0.5/47.6)	3/5	1.4 (0.3/5.7)
Concrete work (177)	5/5	2.3 (0.6/8.0)	4/2	4.2 (0.8/23.7)	1/2	1.3 (0.1/14.1)
Canned/preserved fruits and vegetables (203)	9/12	1.7 (0.7/4.0)	5/8	1.3 (0.4/4.0)	4/3	3.5 (0.8/16.0)
Sugar and confectionery products (206)	4/4	1.9 (0.5/7.7)	3/3	2.0 (0.4/10.2)	1/0	
Tires and inner tubes (301)	4/4	2.0 (0.5/8.1)	4/2	4.2 (0.8/23.5)	0/1	
Concrete, gypsum, and plaster products (327)	9/9	2.2 (0.9/5.6)	6/4	3.2 (0.9/11.6)	3/5	1.3 (0.3/5.7)
Metal work machinery and equipment (354)	5/4	2.5 (0.7/9.6)	2/1	3.9 (0.3/43.6)	2/3	1.3 (0.2/8.1)
Motor vehicles and motor vehicle equipment (371)	7/8	1.8 (0.7/5.1)	5/4	2.8 (0.8/10.7)	2/3	1.1 (0.2/7.2)
Retail stores, not elsewhere classified (599)	4/5	1.7 (0.5/6.4)	3/3	2.2 (0.4/10.8)	1/2	1.0 (0.1/11.7)
Real estate (65)	13/21	1.3 (0.6/2.6)	7/15	1.0 (0.4/2.5)	6/4	3.0 (0.8/10.7)
Amusement and recreation services (79)	17/20	1.7 (0.9/3.3)	12/16	1.5 (0.7/3.2)	5/4	2.7 (0.7/10.2)
Nursing and personal care facilities (805)	4/4	1.9 (0.5/7.9)	2/2	1.9 (0.3/13.5)	2/1	4.3 (0.4/47.7)
Private households (88)	4/5	1.7 (0.5/6.6)	2/2	2.4 (0.3/16.9)	2/3	1.4 (0.2/8.3)
Environmental quality and housing (95)	8/8	2.3 (0.8/6.3)	6/5	2.5 (0.8/8.4)	2/3	1.9 (0.3/11.5)

^aAdjusted for age, state of residence, proxy interview, post-secondary education, pesticides, hair dyes, smoking, and first degree relative with a lymphatic or hematopoietic tumor.

services; hospitals; miscellaneous services; and accounting, auditing, and book-keeping. The occupations of financial insurance and real estate managers, lodging and related service occupations, workers in miscellaneous service occupations; building and related services, janitors, and truck drivers (light) also experienced a significantly increased risk of leukemia.

Tables II and III present industries or occupations with four or more exposed cases where ORs for leukemia were ≥ 2.0 for overall risks or for one of the duration categories, but where the ORs were not statistically significant. ORs of 2.0 or greater for all subjects occurred for workers employed in the following industries: masonry, stonework, tile, and plastering; concrete work; tires and inner tubes; concrete,

TABLE III. Risk ($OR^{\pm 2.0}$) of Leukemia by Duration of Employment in Occupation (Based on Four or More Exposed Cases) Among Cases and Controls From Iowa and Minnesota

Job title (DOT code)	All subjects		> 10 years		≥ 10 years	
	Ca/Co	OR ^a (95%CI)	Ca/Co	OR ^a (95%CI)	Ca/Co	OR ^a (95%CI)
Architecture, engineering and surveying (00/01)	14/38	0.8 (0.4/1.6)	7/7	2.4 (0.8/7.1)	7/29	0.5 (0.2/1.2)
Occupations in life sciences (4)	4/5	2.0 (0.5/7.4)	1/2	1.2 (0.1/12.9)	3/3	2.9 (0.6/14.9)
Law and jurisprudence (11)	5/6	2.0 (0.6/6.7)	2/2	2.2 (0.3/15.9)	3/4	1.8 (0.4/8.1)
Religion and theology (12)	8/9	2.2 (0.8/5.9)	1/2	1.3 (0.1/14.6)	7/7	2.2 (0.7/6.6)
Manufacturing industry managers (183)	10/11	2.1 (0.9/5.0)	4/5	1.9 (0.5/7.2)	6/6	2.2 (0.7/6.9)
Miscellaneous clerical (24)	10/24	1.0 (0.5/2.1)	4/18	0.6 (0.2/1.7)	6/5	2.6 (0.8/8.7)
Vending and door-to-door salesmen (291)	5/4	2.7 (0.7/10.3)	2/2	2.1 (0.3/15.6)	2/2	2.6 (0.4/18.8)
Plant-farming occupations (40)	27/38	1.5 (0.9/2.4)	13/24	1.2 (0.6/2.3)	14/14	2.0 (0.9/4.3)
Or refining and foundry occupations (51)	8/19	0.9 (0.4/2.1)	4/16	0.6 (0.2/1.8)	3/3	2.0 (0.4/10.2)
Occupations in processing of paper and related materials (53)	5/2	4.3 (0.8/22.8)	3/2	2.7 (0.4/16.6)	1/0	

^aAdjusted for age, state of residence, proxy interview, post-secondary education, pesticides, hair dyes, smoking, and first degree relative with a lymphatic or hematopoietic tumor.

gypsum, and plaster products; metalwork machinery and equipment; and administration of environmental quality and housing (Table II). Canning, real estate, amusement and recreation services, and nursing facilities were the only industries with ORs of 2.0 or greater for those with ≥ 10 years of employment. Occupations with ORs of 2.0 or greater for all subjects include life sciences, law and jurisprudence, religion and theology, manufacturing industry managers, vending and door to door salesmen, and occupations in paper processing and related materials (Table III). Miscellaneous clerical, plant-farming occupations, and ore refining and foundry occupations also showed an increased risk for those with ≥ 10 years of employment. Other a priori occupations, which have been previously associated with the risk of leukemia, include painting, plastering, waterproofing, and related occupations (OR ≈ 1.7 , 95% CI: 0.7–4.2 for those working for 10 or more years), and metal-working occupations (OR ≈ 1.5 , 95% CI: 0.8–2.7, data not shown).

The statistically significant associations for histological types of leukemia are presented for industry and for occupation in Table IV and V, respectively. AML was significantly associated with transportation equipment manufacturing, particularly motor vehicles and motor vehicle equipment; health services, particularly working in hospitals; miscellaneous services, particularly working in accounting, auditing, and bookkeeping; as well as working as a financial insurance and real estate manager. CML was significantly associated with industries including sales of nondurable goods (e.g., paints, varnishes and supplies); miscellaneous retail; business services; miscellaneous services; executive and legislative; working in medicine and health; and miscellaneous sales occupations. ALL was significantly associated with industries of railroad transportation, food stores, social services, working in miscellaneous professional and sales occupations, production and stock clerks, and painting, plastering, waterproofing. CLL was significantly associated with industries producing concrete, gypsum, and plaster products; miscellaneous nondurable goods; building materials and garden supplies; amusement and recreation services; health services, particularly in hospitals; national security and internal affairs; and working as manufacturing industry managers, lodging, and related service persons, or janitors. Myelodysplasia was significantly associated with mining and quarrying of nonmetallic minerals; plumbing, heating, and air conditioning; sales of nondurable goods; finance, taxation, and monetary policy; or working as miscellaneous professionals; sales occupations; metal fabricating occupations; and truck drivers.

Risks by histological type of leukemia and by intensity of specific exposures from selected occupational factors are displayed in Table VI. There is some indication that risk may vary by histological type of the disease although

numbers are quite small in most higher exposure categories. ORs of 1.5 or greater with at least two histologically specific cases occurred for AML with exposure to live plants other than in agriculture, working as sick people or children; for CML and exposure to formaldehyde, metals, ionizing radiation; meats, medical profession; and sick people; for ALL with exposure to electromagnetic radiation; and human contacts; for CLL with exposure to meats; and working in the medical professions; or as teachers; and for myelodysplasia with exposure to benzene, motor vapor and exhausts, and live plants. We also evaluated risk by histological type of leukemia and by intensity of exposure for occupational exposure to wood dusts, asbestos, synthetic oils, cooking oils, asphalt and creosote, other solvents, and live cattle. No significant increased risk was found associated with these exposures for any type of leukemia (data not shown).

For specific exposures, analyses were also conducted by probability of exposure, a combination of probability and intensity of exposure, a combination of intensity and duration of exposure, and time since first exposure. This uncovered no notable additional findings (data not shown), except for a significantly increased risk of acute lymphocytic leukemia associated with asbestos exposure (OR ≈ 6.6 , 95% CI: 1.6–26.1), and acute myeloid leukemia for plant exposure (OR ≈ 2.1 , 95% CI: 1.1–4.0).

DISCUSSION

This study provided an opportunity to evaluate relationships between leukemia and occupational exposures while controlling for other risk factors and to consider risks for specific histologic types. An increased risk of leukemia was found for agricultural service industries and plant farming occupations, consistent with findings from earlier epidemiological studies linking agricultural pesticide exposures with elevated risk of leukemia [Blair et al., 1985; Brown et al., 1990].

A significantly increased risk of leukemia was observed among those who worked in health services and in hospitals, and a nonsignificantly increased risk was found for nursing and personal care facility workers. Previous epidemiological studies have reported an increased risk of leukemia among healthcare workers, including nurses, pharmacists, laboratory technicians, and clinical laboratory technicians [Peipins et al., 1997; Burnett et al., 1999; Petralia et al., 1999]. Exposures among healthcare workers are complex, including suspected and established leukemogens, such as ionizing radiation [Lunn, 1987], antineoplastic drugs [Skov et al., 1992], formaldehyde [Blair et al., 1990], and unidentified infectious agents [Alexander et al., 1999; Smith et al., 1998]. Exposure to anesthetic gases and ethylene oxide are also thought to increase the risk of leukemia [Hogstedt et al., 1986]. Subjects employed in miscellaneous

TABLE IV. Statistically Significant Association for Histological Types of Leukemia by Industry (based on seven or more exposed cases) Among Cases and Controls from Iowa and Minnesota

Industry (SIC code)	Controls	AML		OML		ALL		CLL		DYS	
		Ca	OR ¹ (95% CI)	Ca	OR ¹ (95% CI)	Ca	OR ¹ (95% CI)	Ca	OR ¹ (95% CI)	Ca	OR ¹ (95% CI)
Nonmetallic minerals, except fuels (14)	9	1	1.1(0.1/9.1)	0		0		4	2.4(0.7/8.1)	2	5.9(1.2/30)
Plumbing, heating, and air conditioning (171)	18	1	0.4(0.1/3.4)	1	1.4(0.2/11)	0		8	2.1(0.9/5.1)	3	4.0(1.1/15)
Concrete, gypsum, and plaster products (327)	9	1	0.6(0.1/5.3)	0		0		8	5.5(2.0/15.4)	0	
Transportation equipment (37)	40	11	2.3(1.1/4.8)	3	1.9(0.6/6.7)	0		9	1.0(0.5/2.1)	3	1.0(0.3/3.4)
Motor vehicles and motor vehicle equipment (371)	8	4	3.9(1.0/14.7)	0		0		1	0.5(0.1/4.2)	2	4.2(0.7/25)
Railroad transportation (40)	61	9	1.3(0.6/2.8)	3	1.3(0.4/4.5)	2	5.3(1.0/28)	15	12 (0.7/23)	4	11 (0.4/34)
Miscellaneous nondurable goods (519)	16	3	1.5(0.4/5.5)	4	6.8(2.1/22)	0		7	2.6(1.0/6.6)	3	4.7(1.1/20)
Building materials and garden supplies (52)	48	3	0.5(0.1/1.5)	3	1.8(0.5/6.2)	0		16	1.8(1.0/3.2)	1	0.3(0.0/2.1)
Food store (54)	68	5	0.7(0.3/1.7)	3	1.1(0.3/3.7)	3	6.8(1.7/28)	8	0.5(0.2/1.0)	4	1.0(0.3/3.0)
Miscellaneous retail (59)	58	7	1.0(0.4/2.3)	6	2.8(1.1/7.0)	0		11	1.0(0.5/1.9)	2	0.7(0.2/2.9)
Business services (73)	37	5	1.3(0.5/3.6)	5	3.7(1.3/10)	0		3	0.4(0.1/1.3)	1	0.8(0.1/6.2)
Amusement and recreation services (79)	20	5	2.2(0.8/6.1)	0		0		10	2.2(1.0/4.8)	1	1.0(0.1/7.5)
Miscellaneous amusement services (799)	7	2	2.6(0.5/13.9)	0		0		8	4.1(1.4/12)	1	3.3(0.4/29)
Health services (80)	33	12	2.8(1.4/5.9)	1	1.0(0.1/7.5)	0		14	2.2(1.1/4.3)	1	0.4(0.1/3.1)
Hospitals (806)	23	9	2.9(1.3/6.8)	1	1.4(0.2/11)	0		12	2.8(1.3/5.9)	0	
Social services (83)	15	4	1.6(0.5/5.1)	1	1.4(0.2/11)	3	19(4.2/87)	1	0.3(0.0/2.7)	0	
Miscellaneous services (89)	13	9	6.6(2.5/17)	3	8.4(2.1/34)	0		2	1.1(0.2/5.2)	1	1.6(0.2/14)
Accounting, auditing, and book-keeping (893)	6	7	9.3(2.8/30)	0		0		1	1.3(0.1/11.3)	0	
Executive, legislative, and general (91)	47	6	1.1(0.4/2.7)	5	3.1(1.1/8.4)	1	2.4(0.3/21)	8	0.9(0.4/1.9)	2	0.7(0.2/3.0)
Finance, taxation, and monetary policy (93)	33	2	0.4(0.1/1.6)	0		0		7	1.2(0.5/2.8)	5	3.2(1.1/9.1)
National security and internal affairs (97)	423	39	0.6(0.4/5.9)	18	0.9(0.5/1.7)	5	0.9(0.3/2.9)	89	1.3(1.0/1.9)	25	1.7(0.9/3.1)

¹Adjusted for age, state of residence, proxy interview, post-secondary education, pesticides, hair dyes, smoking and first degree relative with lymphatic or hematopoietic tumor.

TABLE V. Statistically Significant Association for Histological Types of Leukemia by Occupation (Based on Seven or More Exposed Cases) Among Cases and Controls From Iowa and Minnesota

Occupation (SOC code)	Controls	AML		CML		ALL		CLL		DYS	
		Ca	OR ^y (95%CI)	Ca	OR ^y (95%CI)	Ca	OR ^y (95%CI)	Ca	OR ^y (95%CI)	Ca	OR ^y (95%CI)
Medicine and health (7)	26	2	0.4(0.1/1.9)	3	4.4(1.2/16.8)	0		5	16(0.6/4.3)	2	0.8(0.2/4.0)
Manufacturing industry managers (183)	11	1	1.0(0.1/8.3)	2	4.5(0.9/22.6)	0		6	2.9(1.0/8.6)	0	
Financial insurance real estate managers (186)	11	8	5.6(2.0/14.8)	1	3.8(0.4/32)	1	5.5(0.3/90.2)	2	1.5(0.3/7.1)	1	1.4(0.1/14)
Miscellaneous professionals (19)	34	3	0.8(0.2/2.7)	2	1.6(0.4/7.5)	2	12.0(1.8/81.4)	4	0.6(0.2/1.7)	4	3.5(1.1/11.1)
Computing and account-recording (21)	43	9	1.8(0.8/4.0)	4	3.0(1.0/9.2)	1	0.7(0.1/7.8)	7	0.9(0.4/2.1)	0	
Production and stock clerks (22)	67	4	0.5(0.2/1.5)	1	0.3(0.0/2.1)	4	6.0(1.3/27)	7	0.5(0.2/1.2)	1	0.4(0.1/2.8)
Sales occupations, consumable (26)	31	4	1.1(0.4/3.3)	1	1.0(0.1/7.8)		0	2	0.4(0.1/1.5)	5	2.8(1.0/7.8)
Miscellaneous sales occupations (29)	81	8	1.0(0.4/2.1)	8	2.6(1.1/5.9)	3	5.0(1.0/24)	14	0.8(0.4/1.5)	2	0.5(0.1/2.0)
Lodging and related service occupations (32)	5	2	2.3(0.4/12.6)	0		0		5	5.0(1.3/19.1)	0	
Miscellaneous occupations (35)	12	2	1.6(0.3/7.9)	0		0		8	3.5(1.4/9.0)	0	
Janitors (382)	35	5	1.2(0.4/3.1)	2	1.3(0.3/5.7)	0		14	2.1(1.1/4.2)	4	1.7(0.6/5.2)
Occupations in metal fabricating (80)	45	6	1.0(0.4/2.5)	4	2.4(0.8/7.1)	0		4	0.4(0.1/1.2)	6	3.0(1.1/7.6)
Painting, plastering, and waterproofing (84)	22	4	1.9(0.6/5.9)	0		2	8.4(1.4/51.3)	7	1.3(0.5/3.2)	1	1.1(0.1/8.9)
Truck drivers, light (906)	8	1	1.2(0.1/10)	2	3.2(0.6/18)	0		5	3.0(0.9/10.0)	3	9.4(2.1/42)
Occupations in extraction of minerals (93)	24	1	0.3(0.0/2.3)	0		1	11.2(1.0/126)	7	1.5(0.6/3.5)	3	2.0(0.5/7.6)

^yAdjusted for age, state of residence, proxy interview, post-secondary education, with lymphatic or hematopoietic tumor.

TABLE VI. Risk for Histological Types of Leukemia by Selected Exposures Among Cases and Controls from Iowa and Minnesota

Exposure	Controls	Total		AML		CML		ALL		CLL		DYS	
		Ca	OR ^y (95%CI)	Ca	OR ^y (95%CI)	Ca	OR ^y (95%CI)	Ca	OR ^y (95%CI)	Ca	OR ^y (95%CI)	Ca	OR ^y (95%CI)
Benzene													
Low	282	121	0.9 (0.7/1.1)	30	0.8 (0.5/1.3)	11	0.9 (0.4/1.8)	3	0.7 (0.2/2.5)	50	0.8 (0.6/1.2)	12	0.7 (0.4/1.4)
High	19	10	1.0 (0.5/2.3)	3	1.1 (0.3/3.9)	0		0		3	0.8 (0.2/2.9)	3	2.6 (0.7/9.7)
Formaldehyde													
Low	128	61	1.0 (0.7/1.4)	14	0.9 (0.5/1.6)	7	1.3 (0.6/3.1)	0		29	1.2 (0.7/1.8)	6	0.8 (0.3/1.9)
High	9	3	0.7 (0.2/2.6)	0		1	2.9 (0.3/24.5)	0		1	0.6 (0.1/5.3)	0	
Paints													
Low	193	85	0.9 (0.7/1.2)	26	1.1 (0.7/1.8)	10	1.3 (0.6/2.8)	2	1.0 (0.2/4.7)	29	0.7 (0.5/1.1)	8	0.7 (0.3/1.5)
High	28	12	0.9 (0.5/1.8)	3	1.0 (0.3/3.3)	1	0.8 (0.1/6.5)	1	2.3 (0.2/22.8)	6	1.1 (0.4/2.7)	0	
Metals													
Low	353	157	0.9 (0.7/1.1)	37	0.8 (0.5/1.2)	11	0.6 (0.3/1.3)	5	1.0 (0.3/3.4)	62	0.8 (0.6/1.1)	22	1.2 (0.7/2.1)
High	28	11	0.8 (0.4/1.6)	3	0.7 (0.2/2.6)	3	2.1 (0.6/7.7)	0		5	0.9 (0.3/2.4)	0	
Solder													
Low	260	99	0.8 (0.6/1.0)	27	0.8 (0.5/1.2)	9	0.7 (0.3/1.6)	4	1.0 (0.3/3.5)	40	0.7 (0.5/1.1)	7	0.4 (0.2/1.0)
High	3	1	0.7 (0.1/7.3)	0		0		0		1	2.3 (0.2/24.3)	0	
Ionizing radiation													
Low	31	14	1.0 (0.5/1.9)	2	0.5 (0.1/2.2)	2	1.8 (0.4/7.9)	0		7	1.4 (0.6/3.4)	1	0.5 (0.1/3.8)
High	3	0		0		0		0		0		0	
Electromagnetic radiation													
Low	222	96	0.9 (0.7/1.2)	21	0.7 (0.4/1.1)	6	0.6 (0.2/1.4)	4	2.4 (0.7/8.8)	43	1.0 (0.7/1.5)	9	0.7 (0.3/1.4)
High	50	13	0.5 (0.1/0)	1	0.2 (0.0/1.2)	3	1.1 (0.3/3.9)	1	1.5 (0.1/15.3)	8	0.8 (0.4/1.7)	0	
Motor vapor and exhausts													
Low	409	187	1.0 (0.8/1.2)	46	0.9 (0.6/1.4)	16	0.8 (0.4/1.5)	5	1.0 (0.3/3.7)	75	0.9 (0.7/1.3)	20	1.0 (0.6/1.8)
High	102	60	1.3 (0.9/1.9)	10	0.9 (0.5/1.9)	5	1.0 (0.4/2.8)	1	1.4 (0.2/13.1)	32	1.4 (0.9/2.3)	7	1.6 (0.7/3.9)
Live plants other than agriculture													
Low	177	97	1.2 (0.9/1.6)	17	0.9 (0.5/1.5)	7	0.9 (0.4/2.1)	3	1.4 (0.3/5.7)	43	1.2 (0.8/1.8)	17	1.9 (1.0/3.6)
High	53	34	1.3 (0.8/2.0)	12	1.7 (0.8/3.3)	2	0.8 (0.2/3.3)	0		13	1.1 (0.6/2.0)	2	0.7 (0.2/3.1)
Any meats													
Low	22	15	1.4 (0.7/2.7)	3	1.1 (0.3/3.8)	0		0		9	2.0 (0.9/4.4)	0	
High	75	38	1.0 (0.7/1.5)	10	1.0 (0.5/2.1)	5	1.5 (0.6/4.1)	0		18	1.2 (0.7/2.2)	3	0.6 (0.2/2.0)

TABLE VI. (Continued)

Exposure	Controls	Total		AML		CML		ALL		CLL		DYS	
		Ca	OR (95%CI)	Ca	OR (95%CI)	Ca	OR (95%CI)	Ca	OR (95%CI)	Ca	OR (95%CI)	Ca	OR (95%CI)
Medical professions	19	11	14(0.6/3.0)	3	12(0.3/4.2)	2	34(0.7/5.9)	1	3.5(0.3/38.2)	4	14(0.5/4.4)	1	0.9(0.1/7.5)
	14	11	1.7(0.7/3.7)	3	1.6(0.4/5.9)	0		0		7	3.0(1.1/7.9)	0	
Teachers	37	18	1.2(0.6/2.2)	8	2.3(1.0/5.6)	1	1.0(0.1/8.3)	0		7	1.6(0.6/3.9)	0	
	20	7	0.7(0.3/1.7)	3	1.0(0.3/3.5)	0		0		4	1.1(0.4/3.4)	0	
Human contact	254	122	1.0(0.8/1.3)	31	1.0(0.6/1.6)	8	0.8(0.4/1.9)	7	3.1(0.9/11.3)	46	0.9(0.6/1.4)	18	1.2(0.7/2.7)
	181	85	1.0(0.7/1.3)	17	0.7(0.4/1.3)	11	1.5(0.7/3.1)	1	0.6(0.1/5.5)	37	1.0(0.7/1.5)	7	0.7(0.3/1.6)

^aAdjusted for age, sex, residence, education, occupation, pesticides, hair dyes, smoking, and first degree relative with lymphatic or hematopoietic tumor.

personal service occupations who experienced a significantly increased risk of leukemia in this study included three practical nurses, 17 attendants for hospitals, morgues, and related health services and four engaged in miscellaneous service occupations. Subjects employed in these occupations could have also been exposed to factors common to healthcare workers.

An increased risk of leukemia was observed among those employed in building and related service occupations, including working as cleaners, janitors, and building pest control service men. An OR of 2.8 (95% CI: 1.4±5.8) (18 cases) was observed for janitors working for 10 or more years. These workers may be exposed to various chemicals, paints, solvents, pesticides, and cleaning chemicals, while building pest control service men are exposed to pesticides and may be exposed to solvents. Both solvents and pesticides have been associated with elevated risk of leukemia [Blair et al., 1979; Brown et al., 1990; Lynge et al., 1997]. A significantly increased risk of leukemia was also observed among those employed in lodging and related service occupations. These occupations include those who worked as hotel workers and various other housekeepers and house cleaners, who could also be exposed to cleaning chemicals.

We found an increased risk of leukemia for those employed in the miscellaneous nondurable goods industry (Table I), which includes sales of paints, varnishes, and related supplies. Subjects working in painting, plastering, waterproofing, and related occupations also were at increased risk. An increased risk of leukemia among painters has been previously reported. However, the association has not been consistent [Chen and Seaton, 1998]. An increased risk of leukemia has also previously been reported for asbestos-exposed workers [Schwartz et al., 1988]. In this study, we found an increased risk of leukemia for those employed in the plumbing, heating, and air conditioning industries (Table I). Workers in these industries could be exposed to asbestos. A significantly increased risk of acute lymphocytic leukemia was observed for those with exposure to asbestos, based on the analysis of probability of exposure in this study.

Our study found a nonsignificant excess risk among workers in the canning (OR ^ 1.7), and sugar and confectionery industries (OR ^ 1.9) (Table II). Leukemia excesses have been previously reported in the beverage and brewery industries, particularly for chronic myeloid leukemia [Linnet et al., 1988], and among cannery workers [Morton and Marjanovic, 1984], and in the food industry [Blair et al., 1980]. We also found an increased risk of leukemia in the metal-working machinery industry (Table II). Subjects in metal-working occupations also experienced an increased risk in this study. In the histologic evaluations using the job-exposure matrix, higher exposure to metals was associated only with CML.

Working in medical professions or as teachers was associated with an increased risk of AML and CLL. Exposure to plants in a nonagricultural situation was associated with an increased risk of AML and myelodysplasia. These observations are consistent with findings from earlier epidemiologic studies indicating that risk of leukemia associated with occupations and various occupational exposures may vary by histological type of the disease [Blair and White, 1985; O'Brien and Decoupe, 1988; Preston-Martin and Peters, 1988; Schwartz et al., 1988; Brown et al., 1990; Mele et al., 1994; Floderus et al., 1999].

Employment in miscellaneous amusement and recreation services was significantly associated with the risk of leukemia. This industry includes those working in public golf courses, membership sports and recreation clubs, and various amusement parks or services. Employment at golf courses have been associated with an elevated risk of leukemia [Kross et al., 1996], possibly linked with exposure to pesticides. Amusement park workers could also have been exposed to oil, grease, and solvents used to service large amusement ride machinery.

Much of the literature on occupational causes of leukemia is based on small numbers of exposed cases. Studies of the cohort design, which assemble large numbers of subjects employed in a particular industry or occupation, typically generate small numbers of leukemias and it is usually not feasible to estimate risks by cell type. Case-control studies, which assemble a larger number of cases, often with information on cell type, usually have small numbers of leukemia patients employed in any particular occupation.

To help overcome the problem of small numbers in analyses by occupation and industry, we created a job-exposure matrix for a number of agents or groups of agents to explore the risk of leukemia by subtype and by exposure. Job-exposure matrices have proven useful in occupational investigations [Hoar et al., 1980; Stewart et al., 1998]. However, they rely on assumptions, which may not always hold. A study by Dewar et al. [1991] suggested that the use of job-exposure matrices in epidemiologic studies may include considerable more exposure misclassification than a subject-specific exposure analysis, resulting in a loss of statistical power.

Application of the job-exposure matrix revealed no clear link between leukemias and benzene in our study, except for myelodysplasias, although an excess of cases occurred among persons employed in several industries that used benzene, such as the rubber industry (i.e. tires and inner tubes), and paints and varnishes. Historically, benzene was used as a solvent and was interchangeable with several other solvents, creating uncertainty as to its presence in many industries or occupations. Dewar et al. [1991] suggested that the sensitivity for benzene is very low when

a job-exposure matrix is used as a means of assigning exposure to study subjects.

Another potential limitation of this study, is that multiple statistical comparisons were made by occupation (> 150 categories), by industry (> 150 categories), and by exposure categories (27 different categories). Therefore, some significantly elevated ORs would be expected based on chance alone. However, the results relating leukemia risk to the agricultural industry, healthcare workers, and subjects who may have been exposed to various solvents were reasonably consistent within the study and with earlier epidemiological studies.

This study enjoys several advantages that may strengthen the interpretation of its findings. These include the systematic pathological review, and our resulting ability to examine associations by histological type, a relatively large sample size, and availability of information on potential confounders. Use of in-person interviews to collect information on history of lifetime occupation and other major potential risk factors of leukemia provides another strength. Unlike recall of specific exposures to particular chemicals, subjects are generally able to recall their lifetime occupational history. Although associations with employment in particular occupations or industries do not necessarily identify individual exposures, they may point to combinations of exposures, which can be evaluated in future epidemiologic studies [Blair et al., 1993].

In summary, the increased risks of leukemia that we observed among agricultural service industries, nursing and healthcare workers, and metal-working occupations, are consistent with earlier occupational epidemiological studies. An association between leukemia and a few occupations or industries (such as janitors, cleaners, printers, and painters) may suggest a link with potential exposures to solvents or chemicals, but this was not consistent across solvent-related occupations. The increased risk with occupation and industries not observed previously warrants further investigation.

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